CT CURE - EU4HEALTH PROGRAMME

ENSURING THE SUSTAINABILITY OF CT-CURE'S EXPEDITED ASSESSMENT EXPERIENCE FOR MULTINATIONAL CLINICAL TRIALS IN PUBLIC HEALTH EMERGENCIES

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Introduction

The CT-CURE Joint Action Work Package 4 is dedicated to sustainability and aims to consolidate the lessons learned by Member States during the expedited assessment of clinical trial applications related to COVID-19 therapeutics. This initiative, which was highlighted at the European Medicines Agency (EMA) workshop "Lessons Learned on Clinical Trials in Public Health Emergencies," seeks to enhance preparedness for future public health emergencies across the EU/EEA.

Clinical trials play a crucial role in validating innovative medicines and repurposing existing treatments during public health crises. In this context, the randomised clinical trials platform initiated by the RECOVERY Collaborative Group has demonstrated that trials that are authorized early in an emerging crisis deliver the greatest benefits to populations and patients.

However, while these fast-track procedures are essential, they must remain compliant with Regulation (EU) No 536/2014 to ensure the protection of participants' rights, safety, dignity, and well-being. Additionally, the generation of reliable and robust data is paramount. The Clinical Trials Regulation (CTR) underscores the importance of transparency to build public trust and encourage participation, with a commitment to publishing results within one year after the conclusion of a trial, or within six months for pediatric trials.

Outbreak of the COVID pandemic and launch of CT CURE

In March 2020, the World Health Organization (WHO) launched the Solidarity trial to evaluate potential COVID-19 treatments in the early pandemic. However, its implementation across EU/EEA Member States was hindered by varying national legislation under the Clinical Trials Directive 2001/20/EC (CTD). While individual Member States often expedited reviews of COVID-19 clinical trial applications, multinational European research initiatives remained fragmented. This led to multiple, separate trials with different sponsors—primarily academic—each lacking the cross-border coordination necessary to recruit enough participants for meaningful results.

To address this challenge, the Clinical Trials Facilitation and Coordination Group (CTFG), later transformed into the Clinical Trials Coordination Group (CTCG), operating under the Heads of Medicines Agencies (HMA), launched a voluntary initiative in April 2020. This effort brought together 22 national authorities to harmonize reviews based on the Solidarity protocol. Although this collaboration lacked a formal legal framework, it followed a methodology similar to that used in the CTFG's Voluntary Harmonisation Procedure (VHP) for multinational clinical trial applications, but without any legal basis, and highlighted the critical need for a fast-track procedure for clinical trials during public health emergencies.

Following discussions on harmonising accelerated reviews, the CTFG laid the groundwork for the CT-CURE initiative. However, it took over a year for 15 EU Member States to officially launch CT-CURE. Approved as the first EU4Health Joint Action, the project was funded by the European Union's European Health and Digital Executive Agency (HaDEA). CT-CURE aimed to expedite the assessment of applications for multinational clinical trials related to COVID-19 and became operational on 1 February 2022.

By that time, Regulation (EU) No 536/2014 was already in force, and the Clinical Trials Information System (CTIS) had been implemented. This central platform was designed to streamline the submission and joint review of applications by Member States Concerned (MSCs), marking a significant step forward in the EU's coordinated response to public health crises.

Development of the Best Practice and compliance in CT-CURE applications

To shorten the assessment phase of multinational clinical trial applications, the 15 participating Member States agreed on the expedited CT-CURE Best Practice. This process began when the submitted application was declared valid and was divided into two parts: Part I, coordinated by the Reporting Member State (RMS) with input from all involved Member States, and Part II, assessed at the national level by each Member State.

The Best Practice was tested in the CTIS sandbox/training environment, allowing for the development of practical guidance on how to navigate both within and outside the system.

The trial applications reviewed under CT-CURE represented the entire clinical trial lifecycle, including transitions from CTD authorised trials to the CTR approved trials, new trials, the addition of new Member States to an approved trial, and substantial modifications to the approved trials. To ensure predictability in timelines, the RMS set fixed dates for the accelerated sequential assessment subphases. These timelines, including deadlines for the sponsor's response to requests for information, were communicated to stakeholders through email or secure Eudralink links at the end of the application validation phase.

Clinical Trials Regulation - calculation of timelines

Understanding the timelines for CTR application reviews can be complex. The evaluation process is divided into three primary phases: validation, assessment, and decision. Each phase has a legally defined maximum duration, measured in calendar days. In cases where the deadlines are not met, tacit authorization is granted under the CTR.

When it comes to multinational clinical trial applications, predicting timelines becomes even more challenging. The validation and assessment processes are divided into sequential sub-phases, each with its own legally defined maximum duration in calendar days. These sub-phases include the selection and

agreement on the Reporting Member State (RMS), which is responsible for preparing the assessment report and coordinating the multinational review of Part I of the application. Afterward, the MSC submit their considerations, which are consolidated into a Request for Information (RFI).

The following sub-phase allocates time for the sponsor's response to the RFI, a coordinated review by the MSC, and the conclusions drawn by the RMS. If no RFI is issued, the RMS can directly conclude the validation and proceed to the assessment phase. To ensure adherence to these timelines, tacit authorisation remains an important mechanism in the regulatory framework.

Deadlines under the CTR are defined in calendar days, in accordance with Regulation (EEC, Euratom) No 1182/71, which applies to all due dates. If a deadline falls on a weekend or a bank holiday in the RMS for Part I of the assessment, or in any MSC for Part II, the deadline is automatically moved to the next working day. Additionally, no sub-phase can be shorter than two consecutive working days.

To account for the wide variety of national holidays across the EU/EEA, a 16-day winter clock stop has been established, running from December 23 to January 8. This provision extends the main deadlines and their corresponding sub-phases.

To ensure that all deadlines are met within this complex framework, the CTIS has implemented an algorithm that takes public holidays in all Member States into account, helping to streamline the process and maintain compliance.

The CTR sets maximum deadlines for sponsors to respond to RFIs. Upon receiving a validation or evaluation RFI, sponsors must reply by the deadline specified by the RMS—no more than 10 calendar days for a validation RFI and 12 calendar days for an assessment RFI. If these deadlines fall on a weekend or during the winter shutdown, they are shifted to the next working day. Failure to respond within the allotted time results in the application lapsing.

Moreover, when submitting an RFI, the deadlines for validation and evaluation phases are extended to 15 and 31 calendar days, respectively. However, if multiple RFIs are issued during these phases, no further extensions will be granted. Responses to additional RFIs must be provided promptly, as they occur within the review period allocated to defined procedures by both the RMS and MSC.

Figures 1-6 show the timelines for the different application procedures and the CT-CURE shortened assessment timelines for multinational clinical trials.

FIGURE 1

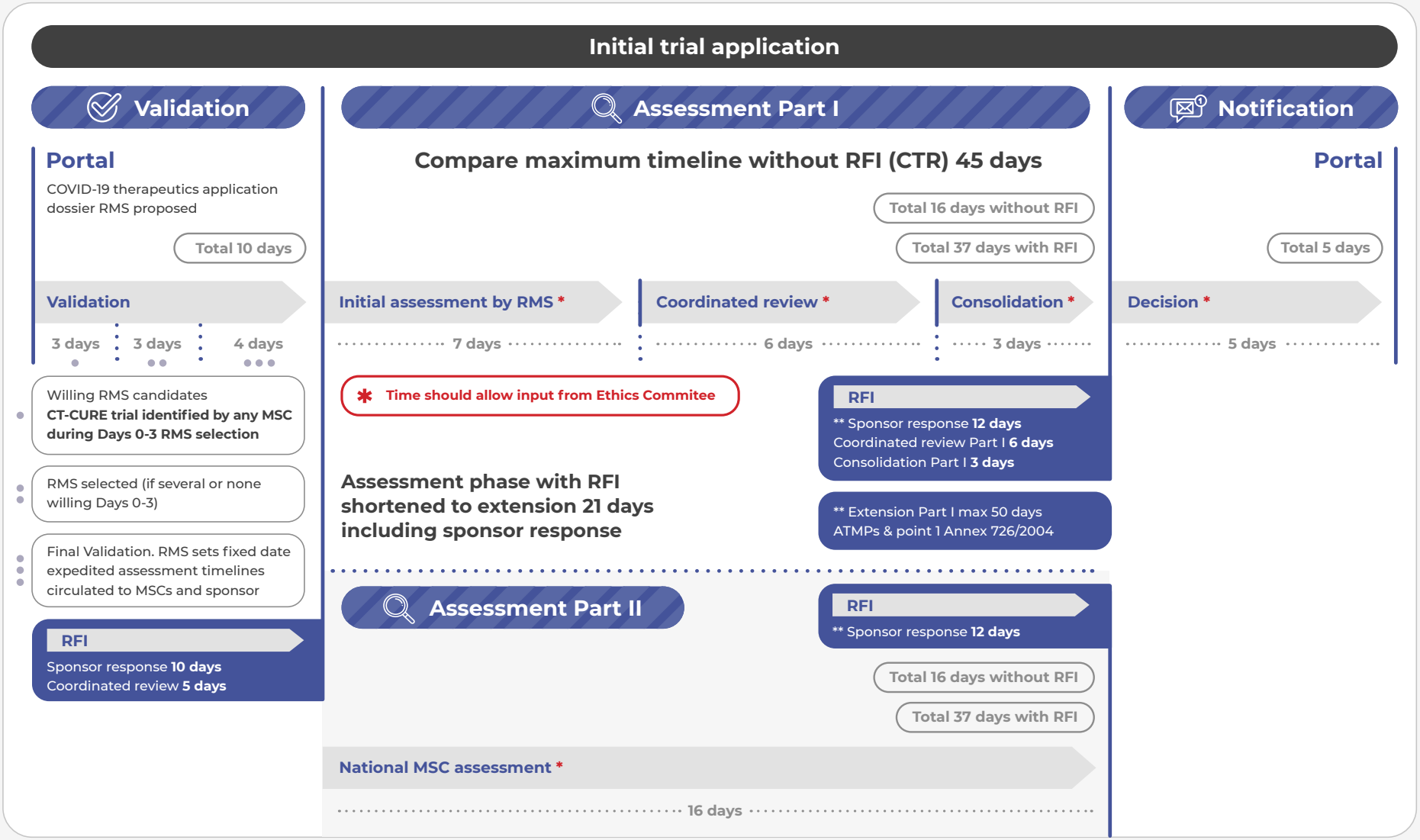

Initial trial application
Validation
Portal
COVID-19 therapeutics application dossier RMS proposed
Total 10 days
Validation
3 days
3 days
4 days
Willing RMS candidates
CT-CURE trial identified by any MSC during Days 0-3 RMS selection
RMS selected (if several or none willing Days 0-3)
Final Validation. RMS sets fixed date expedited assessment timelines circulated to MSCs and sponsor
RFI
Sponsor response 10 days
Coordinated review 5 days
Assessment Part I
Compare maximum timeline without RFI (CTR) 45 days
Total 16 days without RFI
Total 37 days with RFI
Initial assessment by RMS *
7 days
Coordinated review *
6 days
Consolidation *
3 days
* Time should allow input from Ethics Commitee
RFI
** Sponsor response 12 days
Coordinated review Part I 6 days
Consolidation Part I 3 days
Assessment phase with RFI shortened to extension 21 days including sponsor response
** Extension Part I max 50 days
ATMPs & point 1 Annex 726/2004
Assessment Part II
RFI
** Sponsor response 12 days
Total 16 days without RFI
Total 37 days with RFI
National MSC assessment *
16 days
Notification
Portal
Total 5 days
Decision *
5 days

FIGURE 2

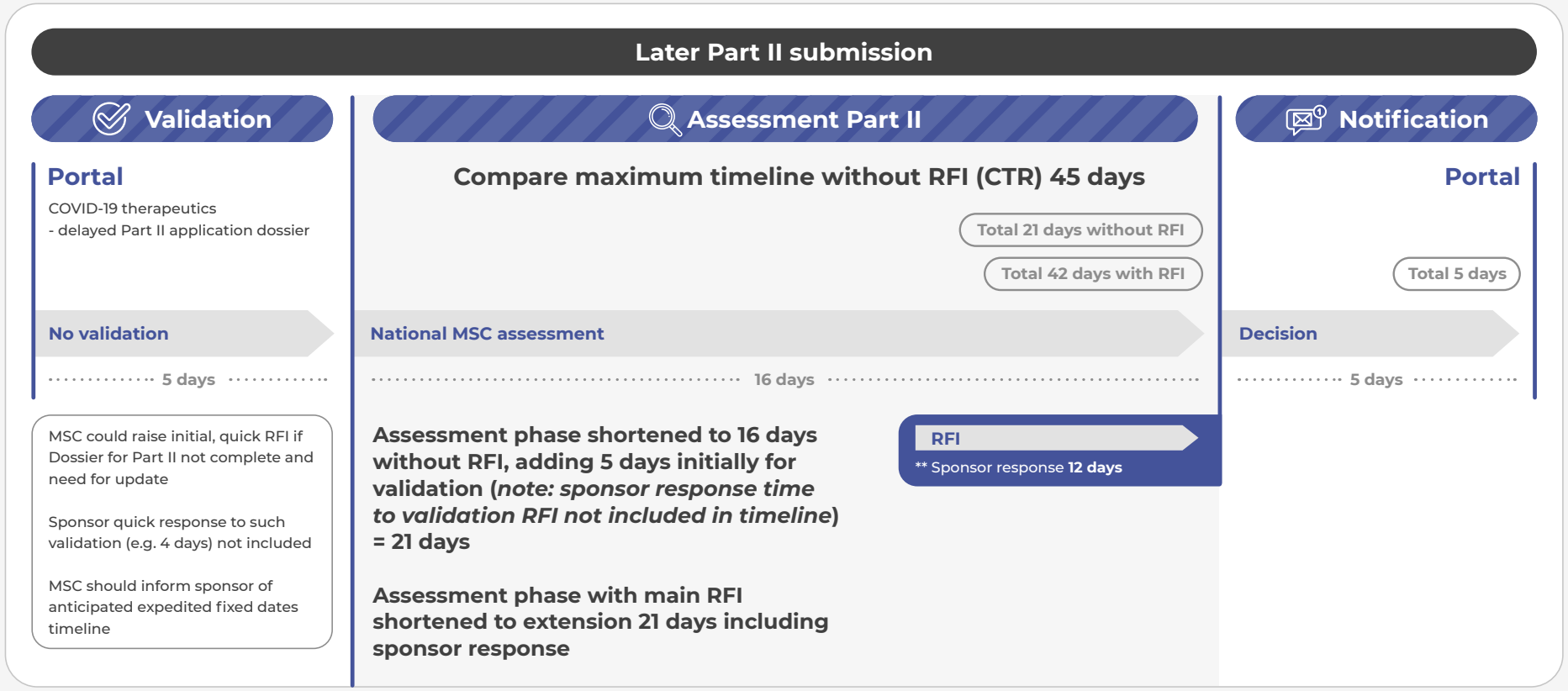

Later Part II submission
Validation
Assessment Part II
Notification
Portal
COVID-19 therapeutics
- delayed Part II application dossier
Compare maximum timeline without RFI (CTR) 45 days
Total 21 days without RFI
Total 42 days with RFI
Portal
Total 5 days
No validation
National MSC assessment
Decision
5 days
16 days
5 days
MSC could raise initial, quick RFI if Dossier for Part II not complete and need for update
Sponsor quick response to such validation (e.g. 4 days) not included
MSC should inform sponsor of anticipated expedited fixed dates timeline
Assessment phase shortened to 16 days without RFI, adding 5 days initially for validation (note: sponsor response time to validation RFI not included in timeline) = 21 days
Assessment phase with main RFI shortened to extension 21 days including sponsor response
RFI
** Sponsor response 12 days

FIGURE 3

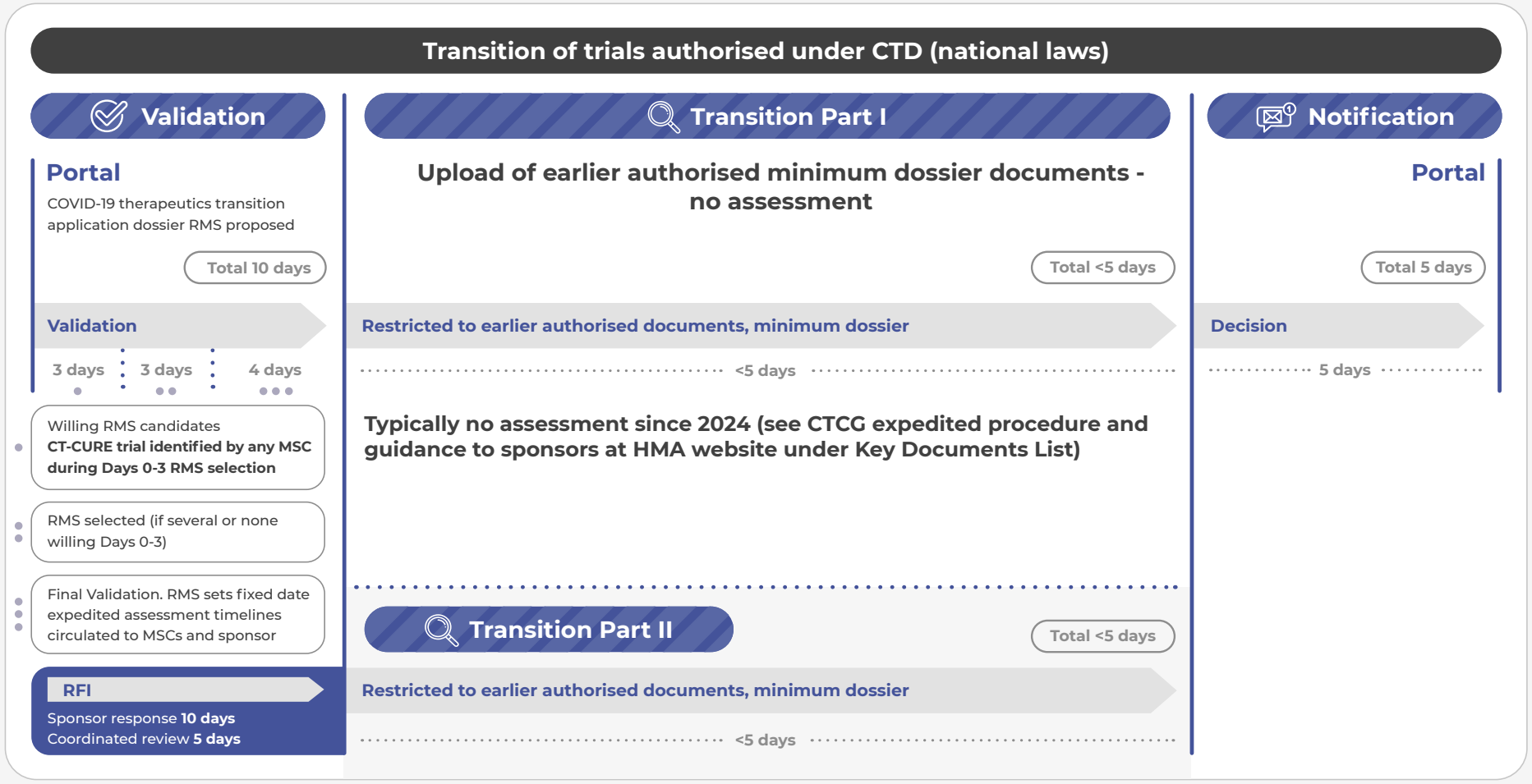

Transition of trials authorised under CTD (national laws)
Validation
Portal
COVID-19 therapeutics transition application dossier RMS proposed
Total 10 days
Validation
3 days
3 days
4 days
Willing RMS candidates CT-CURE trial identified by any MSC during Days 0-3 RMS selection
RMS selected (if several or none willing Days 0-3)
Final Validation. RMS sets fixed date expedited assessment timelines circulated to MSCs and sponsor
RFI
Sponsor response 10 days
Coordinated review 5 days
Transition Part I
Upload of earlier authorised minimum dossier documents - no assessment
Total <5 days
Restricted to earlier authorised documents, minimum dossier
<5 days
Typically no assessment since 2024 (see CTCG expedited procedure and guidance to sponsors at HMA website under Key Documents List)
Transition Part II
Total <5 days
Restricted to earlier authorised documents, minimum dossier
<5 days
Notification
Portal
Total 5 days
Decision
5 days

FIGURE 4

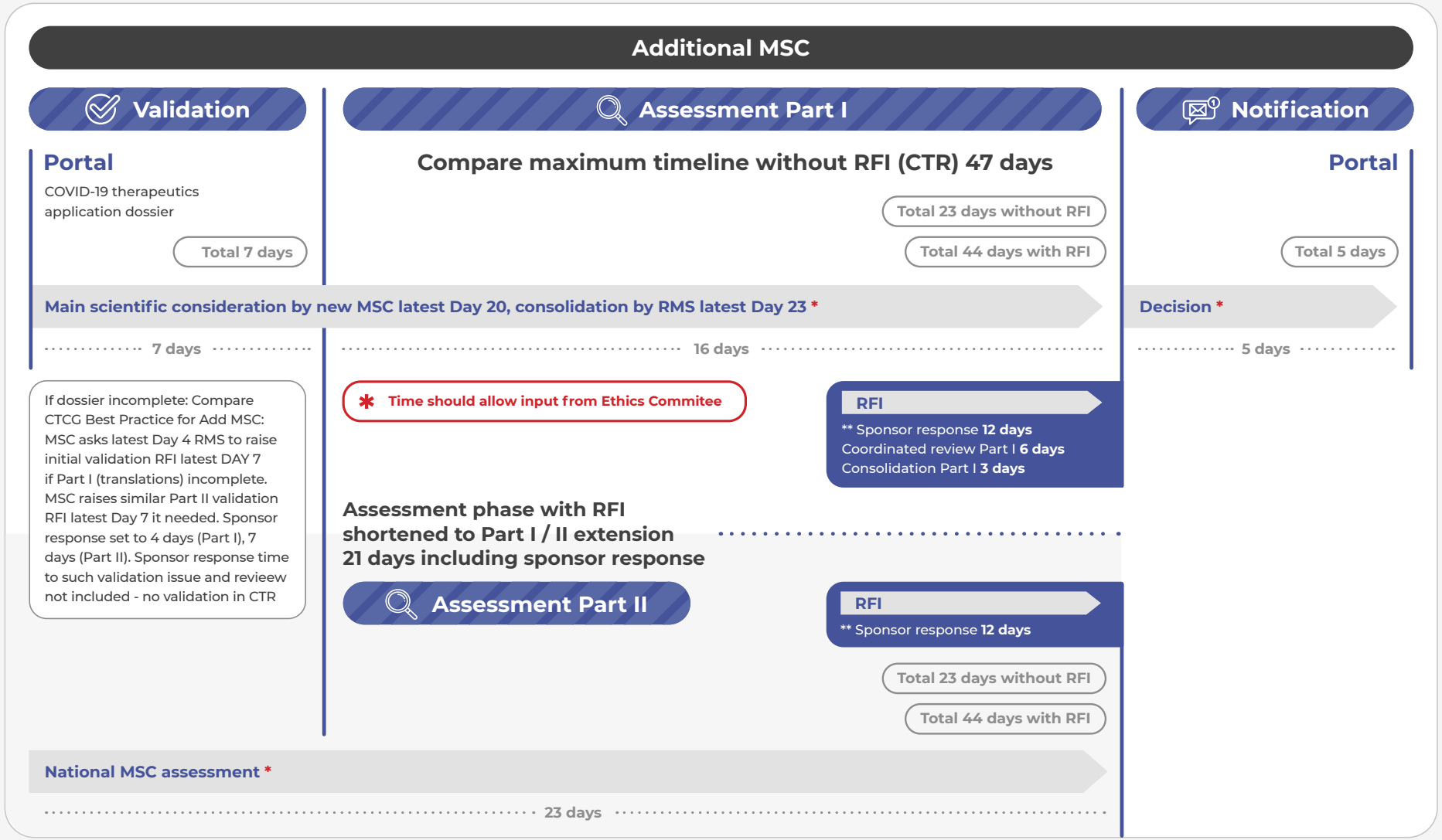

Additional MSC
Validation
Assessment Part I
Notification
Portal
COVID-19 therapeutics application dossier
Total 7 days
Compare maximum timeline without RFI (CTR) 47 days
Total 23 days without RFI
Total 44 days with RFI
Portal
Total 5 days
Main scientific consideration by new MSC latest Day 20, consolidation by RMS latest Day 23 *
Decision *
7 days
16 days
5 days
If dossier incomplete: Compare CTCG Best Practice for Add MSC: MSC asks latest Day 4 RMS to raise initial validation RFI latest DAY 7 if Part I (translations) incomplete. MSC raises similar Part II validation RFI latest Day 7 it needed. Sponsor response set to 4 days (Part I), 7 days (Part II). Sponsor response time to such validation issue and revieew not included - no validation in CTR
* Time should allow input from Ethics Commitee
RFI
** Sponsor response 12 days
Coordinated review Part I 6 days
Consolidation Part I 3 days
Assessment phase with RFI shortened to Part I / II extension 21 days including sponsor response
Assessment Part II
RFI
** Sponsor response 12 days
Total 23 days without RFI
Total 44 days with RFI
National MSC assessment *
23 days

FIGURE 5

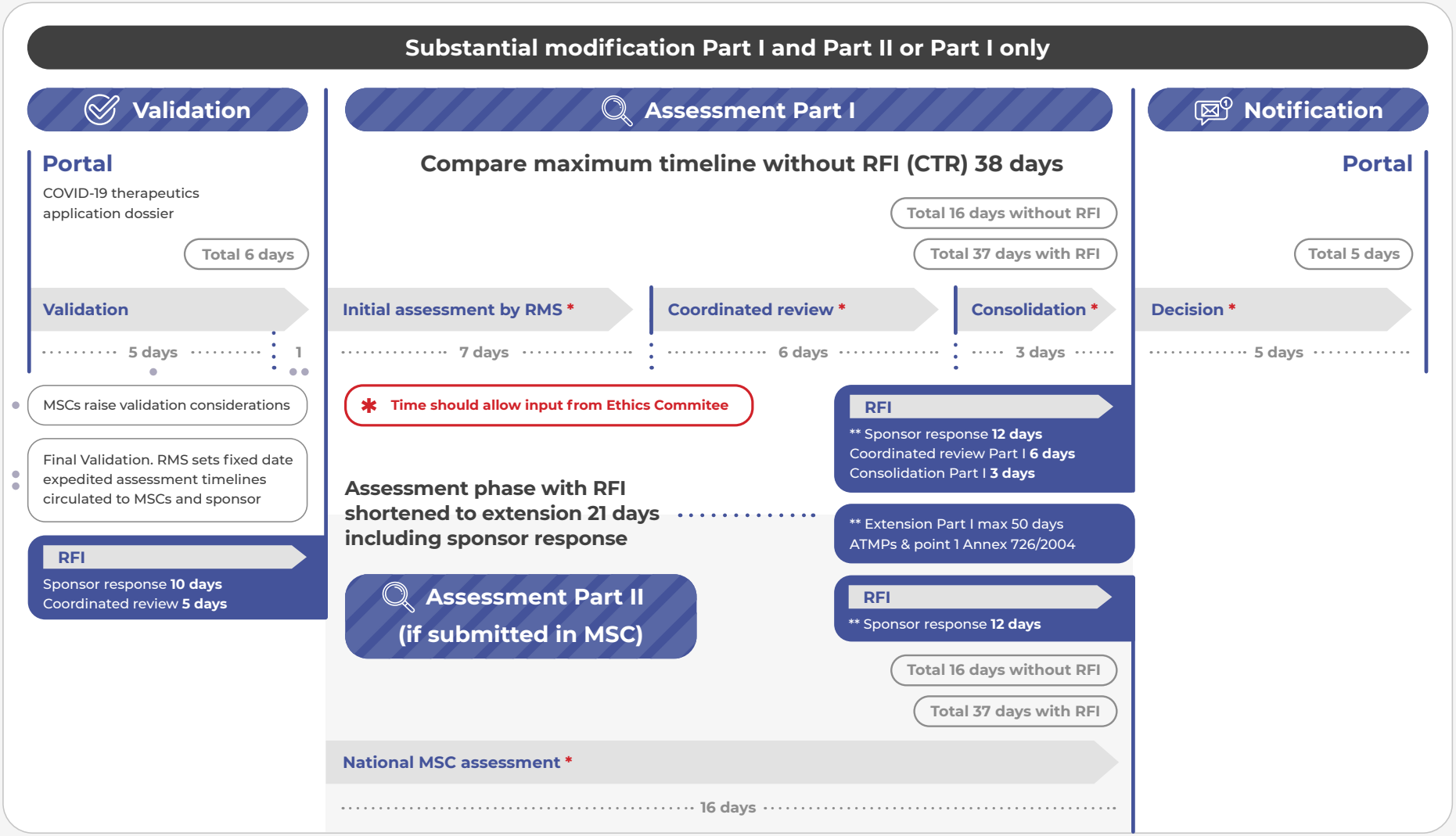
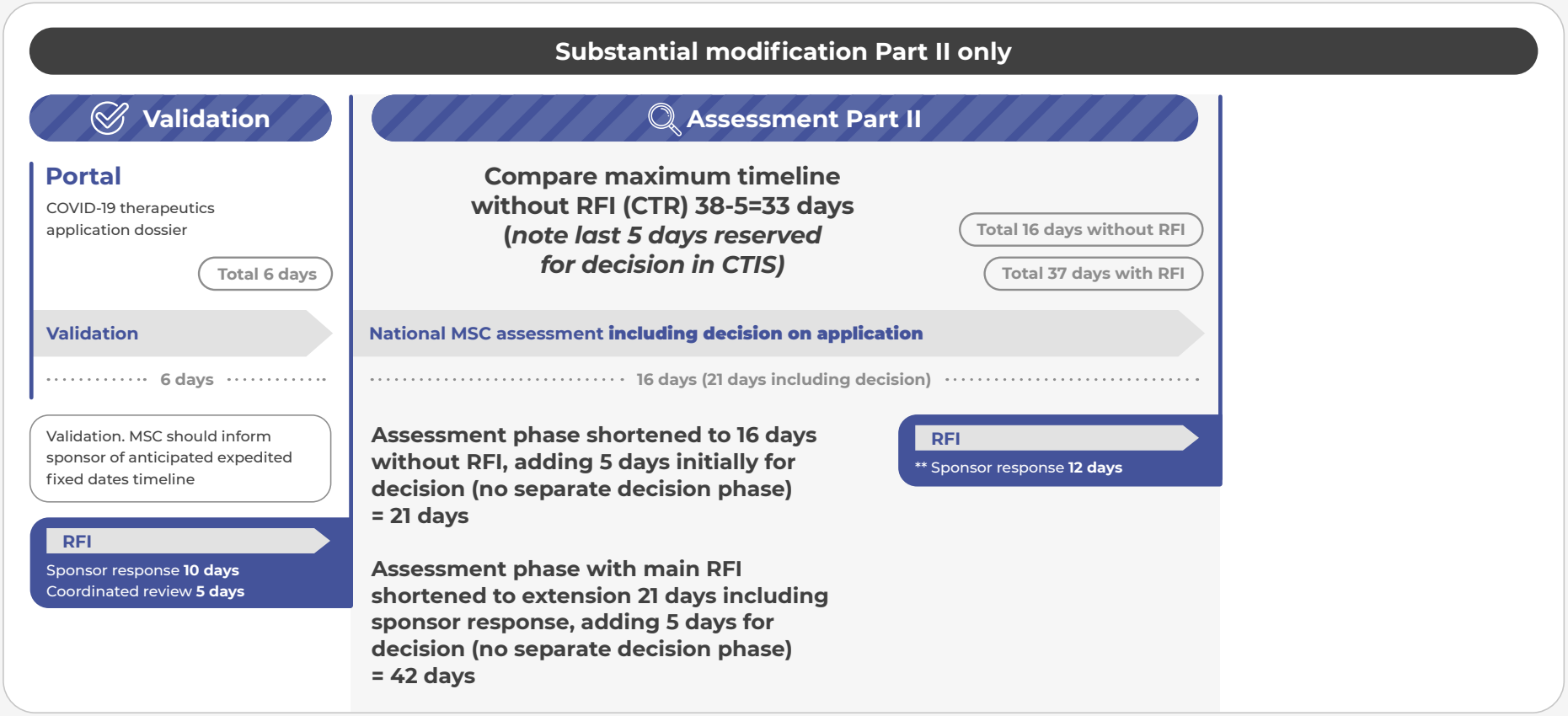

Substantial modification Part I and Part II or Part I only
Validation
Portal
COVID-19 therapeutics application dossier
Total 6 days
Validation
5 days
1
MSCs raise validation considerations
Final Validation. RMS sets fixed date expedited assessment timelines circulated to MSCs and sponsor
RFI
Sponsor response 10 days
Coordinated review 5 days
Assessment Part I
Compare maximum timeline without RFI (CTR) 38 days
Total 16 days without RFI
Total 37 days with RFI
Initial assessment by RMS *
7 days
Coordinated review *
6 days
Consolidation *
3 days
* Time should allow input from Ethics Commitee
RFI
** Sponsor response 12 days
Coordinated review Part I 6 days
Consolidation Part I 3 days
Assessment phase with RFI shortened to extension 21 days including sponsor response
** Extension Part I max 50 days
ATMPs & point 1 Annex 726/2004
Assessment Part II (if submitted in MSC)
RFI
** Sponsor response 12 days
Total 16 days without RFI
Total 37 days with RFI
National MSC assessment *
16 days
Notification
Portal
Total 5 days
Decision *
5 days

FIGURE 6


Substantial modification Part II only
Validation
Portal
COVID-19 therapeutics application dossier
Total 6 days
Validation
6 days
Validation. MSC should inform sponsor of anticipated expedited fixed dates timeline
RFI
Sponsor response 10 days
Coordinated review 5 days
Assessment Part II
Compare maximum timeline without RFI (CTR) 38-5=33 days (note last 5 days reserved for decision in CTIS)
Total 16 days without RFI
Total 37 days with RFI
National MSC assessment including decision on application
16 days (21 days including decision)
Assessment phase shortened to 16 days without RFI, adding 5 days initially for decision (no separate decision phase) = 21 days
Assessment phase with main RFI shortened to extension 21 days including sponsor response, adding 5 days for decision (no separate decision phase) = 42 days
RFI
** Sponsor response 12 days

Compliance with CT-CURE Best Practice timeline

According to Annex I, 11 multinational applications related to COVID-19 therapeutics met the Joint Action Best Practice criteria, despite three being withdrawn by the sponsor. All trials featured complex adaptive designs and were conducted by academic sponsors.

The applications spanned different stages of the trial lifecycle and included four of the six multinational procedures outlined in the Best Practice framework. These involved both CT-CURE MSCs (8 out of 15 EU/EEA Member States) and non-CT-CURE MSCs (7 out of 15 EU/EEA Member States).

While non-CT-CURE MSCs were not always contacted in advance by the sponsor, most adhered to expedited timelines. These timelines were deemed valid, as calendar days were extended in accordance with Regulation (EEC, Euratom) No 1182/71, which sets deadlines in due dates to working days.

The project's first trial was a transition from a multinational clinical trial approved under the CTD, jointly assessed by Member States. It was the first transition trial submitted to the CTIS before the establishment the later agreed harmonised procedure, which does not evaluate applications for trials already approved under the CTD. Initially withdrawn for technical reasons, the trial was resubmitted a month later, encompassing all 14 Member States where it had previously been initiated under the CTD.

The Part I assessment phase averaged eight days post-validation, comparable to Part II for CT-CURE MSCs but longer and more variable for non-CT-CURE MSCs. Notably, despite the RMS being a non-CT-CURE MSC, its assessment phase remained close to the Best Practice recommendation of fewer than five days post-validation.

Majority of COVID-19 trial reviews align with Best Practices, despite variances in Assessment timelines

Seven out of eight completed application reviews adhered to CT-CURE Best Practices for evaluation timelines. It should be noted that, due to the agreed winter clock stop, 16 days were deducted from one substantial modification involving both Parts I and II and one non-CT-CURE RMS. Other timeline extensions under Regulation 1182/71 were minimal—ranging from one to two days—and were not taken into consideration when calculating the length of the assessment phase. Notably, sponsors consistently responded to RFIs within the 12-day limit.

Two applications—one for a substantial modification in Part I and another for a modification covering both Parts I and II—did not include Part I assessment RFIs. However, some procedures accumulated a high number of considerations, reaching up to 70 in trials that introduced an investigational new medicinal product.

In the Part I substantial modification with a non-CT-CURE RMS, the assessment period exceeded the expected 37 days, deviating from the accelerated timeline by 27 calendar days and nearing the maximum allowance under the non-CT-CURE CTR. Additionally, in both the modified transition trial and the substantial modification of Parts I and II involving a CT-CURE RMS, one CT-CURE MSC failed to meet the Part II review target.

While MSCs not participating as members of CT-CURE largely committed to CT-CURE Best Practices, they generally required longer timelines to complete Part II assessments.

CT-CURE streamlined the evaluation process, cutting assessment timelines by over 60% for new, initial trials and approximately 60% for substantial modifications. However, after a RFI, the acceleration appears less pronounced, as spon-

sors were granted the full response period. In contrast to MSCs assessing the applications, sponsors were always granted the maximum time for responses provided in CTR. In procedures without a validation phase—such as a later Part II following the initial Part I only application or the inclusion of an additional MSC—the exact time savings are more challenging to quantify.

According to data available on the public portal, most initial trial applications were authorized, either with or without conditions. Nearly all applications received approval, except for one that was initially rejected by an MSC due to a negative Ethics Committee opinion. This application was subsequently authorized three months later.

Notably, despite this initial rejection, the same MSC was the first to recruit participants, while CT-CURE MSCs took between two and six months after authorization to begin recruitment.

Assessment timelines improve in recent CT-CURE trial applications

Among the three initial applications reviewed—one transitional application with a non-CT-CURE RMS and two initial applications (one with a CT-CURE RMS and one with a non-CT-CURE RMS)—the transitional application with a non-CT-CURE RMS was withdrawn after validation. The remaining two followed the accelerated Part I assessment timelines, completing evaluations in 42 and 38 days after validation for the initial application with a non-CT-CURE RMS and the one with a CT-CURE RMS, respectively.

In Part II, the first trial, submitted in 2022, experienced longer assessment timelines, taking 46 days in CT-CURE MSCs and 56 days in non-CT-CURE MSCs. However, the second trial, submitted in 2024, demonstrated significantly improved efficiency, with assessments completed in 23 days after validation for CT-CURE MSCs and 34 days for non-CT-CURE MSCs.

Additionally, a single Add-MSC application was submitted for a CT-CURE trial in a non-CT-CURE RMS. The Part II assessment adhered to Best Practice guidelines, concluding in 44 days, while the Part I assessment was completed in just 21 days—despite incorporating a request for information during the review process.

Five substantial modification requests were submitted under CT-CURE, one of which was withdrawn after validation. Of the remaining four, three adhered to CT-CURE timelines, while one did not.

The most recent application, with a CT-CURE MSC acting as the RMS, saw a notably swift Part I evaluation, completed in just three days without a RFI. In Part II, the average assessment duration was 16 days for CT-CURE MSCs and 24 days for non-CT-CURE MSCs. However, evaluating Part II timelines remains challenging, as the mixed Part I and Part II application had a Part II submitted to only a few MSCs.

Despite CT-CURE assessment phases being significantly shorter than the maximum legal timelines, prolonged validation phases continued to contribute to extended overall review periods.

Future public health emergency trials – recommendations from CT-CURE

CT-CURE was established by Member States to accelerate the review process for COVID-19 therapeutic applications during the declared public health emergency. While the initiative initially focused on large multinational trial applications, its launch occurred after the most dynamic phase of the pandemic had passed, limiting its immediate impact.

An earlier start for the project would not have been feasible, as the CTIS played a crucial role in the coordinated review of multinational trials under the CTR. The CTR, which provided a unified legal framework for national competent authorities and ethics committees across the EU/EEA, only came into effect on January 31, 2022—six months after the European Commission declared the EU Portal and database fully functional, following an independent audit and approval by the EMA Management Board.

In contrast, mononational trials were approved more quickly both within and outside the EU/EEA. One of the most successful examples was the UK's RECOVERY trial, which rapidly recruited a large number of participants. In March 2020, the non-commercial sponsor consortium drafted the first protocol, submitted an application to the national competent authority and ethics committee, received approval within days, and recruited the first participant—all within two weeks.

The first CT-CURE multinational trial, involving 14 MSCs, was submitted just one week after CTIS and CTR came into force. However, it did not trigger the expected surge in multinational COVID-19 therapeutic trial applications, as the project's late launch meant the peak of the pandemic had already passed.

Strengthening multinational trial coordination and reducing assessment timelines

The primary goal of CT-CURE was to expedite the joint assessment of multinational clinical trials while fostering trust and cooperation between EU/EEA Member States' National Competent Authorities and Ethics Committees. This was made possible by the common legal framework established under the CTR and the implementation of the CTIS.

CT-CURE served as an initial step toward streamlining trial application reviews under the new legal framework, significantly reducing assessment timelines compared to the maximum limits outlined in the CTR (see Annex1 and Best Practice targets in Annex 2). For assessments that included a RFI, where sponsors were granted the full 12-day response period, Member States' assessment timelines were, on average, reduced by 60% for both new initial trial applications and substantial modification applications—after deducting sponsor response time. Notably, the 12-day sponsor response period accounted for approximately 10% of the total expedited CT-CURE assessment timeline when an RFI was involved.

Unlike marketing authorisation application processes, the CTR does not include a clock-stop when sponsors respond to considerations raised, further contributing to the efficiency gains achieved under CT-CURE.

In future public health emergencies, ensuring high-quality application submissions in line with simplified and harmonized rules for the application package could significantly reduce assessment timelines. It would also expedite the

validation phase, which is often prolonged—sometimes up to a month—when MSCs question the completeness of submitted applications.

Currently, sponsors report that non-harmonized requirements and an increased number of documents for the Part II dossier, compared to the CTD, contribute to delays in preparing public health emergency clinical trial applications. Addressing these challenges through simplifications—such as minimizing dossier translation requirements to only those essential for protecting trial subjects' rights and safety (see Annex II of the CTR Questions and Answers adopted by the Clinical Trial Coordination Group (CTAG))—could further enhance efficiency. Structured applications that meet minimum requirements for public health emergency trials would not only streamline the review process but also promote more harmonized evaluation principles, leading to shorter timelines for both Part I and Part II assessments.

CT-CURE Member States also highlighted the need for additional resources beyond normal application processing to maintain compliance with expedited assessments. This included increased staff training and additional support for the EMA CTIS helpdesk to address urgent issues related to application submissions. While the need for assessment RFIs may indicate a lack of clarity on application requirements, it also suggests that Member States are raising an excessive number of considerations. Some CT-CURE applications faced as many as 70 considerations during assessment.

To improve efficiency, Member States must continue implementing the agreed-upon CTCG Best Practice principles, which emphasize that considerations should be limited to issues that are required for an adequate review, including those that could result in a rejection or an authorization with conditions. Additionally, the RMS should take a more stringent approach in consolidating the considerations raised by MSCs. However, failing to forward MSC considerations to sponsors could lead to disputes over the RMS's Part I conclusion, particularly regarding the reliability and robustness of data or the protection of subject rights and safety—grounds for rejection by an MSC outlined in CTR Article 8.2(c) and 8.4. If an ethics committee issues a negative opinion on the Part I conclusion or if critical considerations are omitted, that MSC may reject the trial application. This scenario occurred in one CT-CURE trial.

Despite these challenges, CT-CURE successfully minimized outright application rejections by granting authorizations with conditions. Sponsors were required to address these conditions either through a subsequent substantial modification application or a non-substantial modification, ensuring trials could proceed while meeting regulatory standards.

Seek for a further reduction of deadlines by sponsors

Sponsors often compare the review timelines of CTIS and CTR with the national timelines under the CTD regulatory and ethics review processes. While the expedited timetable under CT-CURE was indeed faster, including both initial applications and trials transitioning from CTD to CTR, sponsors have expressed that the shortened application review, though appreciated, was not sufficient. For instance, while only the assessment phase was expedited, the target timeline for the entire review was reduced by 37% for initial applications that included a RFI. The average timelines for CT-CURE MSCs for initial applications were 25% and 35% shorter compared to the maximum CTR timelines.

However, calculating the range of accelerated timelines for substantial modification applications is more complex, as some MSCs reviewed both Part I and Part II together, while others assessed only Part I in a single application. The most significant acceleration occurred for a substantial modification application without an RFI, which was 65% shorter than the maximum CTR timeline.

While the time allocated for assessing Part I is significantly reduced for the RMS in CT-CURE—just 7 days to prepare the Draft Assessment Report, compared to the CTR's 26 days for initial trial applications—it is essential to ensure the report remains both concise and informative. This enables other MSCs to effectively rely on the document during the expedited coordinated review, which lasts 6 days.

To improve clarity, it is recommended that key aspects of the assessment be summarized at the beginning of the report, followed by a justification of why these aspects are acceptable or not. For significant changes to the dossier, an updated version of the Draft Assessment Report should be issued. This updated report could include key considerations raised by MSCs, particularly those leading to requests for the sponsor to modify the application in response to an RFI, authorizations with conditions, or rejections.

All trials submitted to CT-CURE featured complex, adaptive platform designs, with sponsors generally following the recommendation to seek advice both from the EMA's Emergency Task Force (ETF) and through direct contacts with National Competent Authorities (NCAs) in the countries where the trials were planned. In some cases, sponsors also engaged with the CT-CURE Coordinator.

In one case, a sponsor withdrew its application from all MSCs after receiving multiple validation considerations, choosing to address these issues before resubmission. The gap between the two submissions spanned several months, suggesting the initial submission was used as a foundation for the eventual successful application. Several MSCs reported that discussions regarding the planned trials began months before the official submission, a process that proved resource-intensive, particularly for NCAs. To streamline this, it would be beneficial if sponsors could notify MSCs of their intent to conduct trials at least two weeks before submitting the application.

Once submitted, most communication took place within CTIS, although Member States still needed to communicate via secure external links. For improved coordination, especially where the RMS communicated Part I expedited subphase timelines to MSCs and the sponsor, it is recommended that this communication be fully integrated into CTIS in the future.

Finally, establishing predefined, fixed dates for the assessment timetable is crucial to ensure all parties—including MSC NCAs, ethics committees, and sponsors—have sufficient predictability and clarity throughout the entire Part I application review process. This means that timelines remain as predicted, even if an earlier assessment phase is finalised before the due date.

Effective coordination of Part I assessments in multinational trials requires additional functionalities within CTIS. Key among these enhancements is the ability to manage situations where more than one assessment RFI needs to be sent to the sponsor. Several application procedures (see footnotes Annex 2) currently lack clearly defined review phases for validation in both the CTR and CTIS. For these procedures, an initial RFI with a short response time may indicate that the application is incomplete. Multiple, sequential RFIs are not among functionalities supported in CTIS.

While the ideal application review process involves the RMS sending a single scientific RFI with considerations to the sponsor, some flexibility is necessary when further clarification of a sponsor's response is required to prevent rejection or conditional authorization. However, multiple RFIs can create challenges, particularly for ethics committees, who often plan discussions of applications during regular meetings. Therefore, additional RFIs should not introduce new scientific issues related to the content of the dossier.

To better handle public health emergencies, CT-CURE recommends several CTIS enhancements. For example, it would be beneficial for MSCs to indicate when they have completed the review of a second RFI, thus avoiding the need

for email communication with the RMS. Furthermore, CT-CURE Member States strongly advocate for the RMS to set due dates for Part I subphase assessments in CTIS, signaling to sponsors and MSCs that timelines are planned to be shorter than the maximums allowed under CTR. A similar tool for MSCs would be valuable for the Part II assessment process.

Calling for broader collaboration in communication and dissemination for future health emergencies

The CT-CURE Work Package on Communication and Dissemination must ensure ongoing involvement from clinical trial experts across Member States, including groups like the CTCG and MedEthicsEU, alongside the CTAG. In line with this role, the final version of the CT-CURE Best Practice guidelines has been published on the CTCG/HMA website. The CT-CURE Consortium concluded that while sponsors had full transparency of the evolving Best Practice versions throughout the project, a separate guidance or set of recommendations specifically for sponsors should be developed. Additionally, it is crucial that all networks of clinical trial experts within National Competent Authorities and Ethics Committees are engaged to enhance preparedness for future public health emergencies. This goal is now a priority within the ACT-EU framework.

Members of the CT-CURE Consortium have called for increased flexibility in application submissions, either through modifications to the CTIS or via widely agreed, efficient workaround procedures. One suggestion is that initial applications be prepared in advance of a public health emergency, involving all EU/EEA Member States where the trial is planned. This would mean that, in line with CTR, MSCs receive only a Part I application and that these MSCs are all included in subsequent substantial modifications for Part I. Additionally, the consortium recommends further flexibility for sponsors seeking to add new trial sites in MSCs that authorized the initial application, as well as extending authorization to new MSCs beyond the original ones. This approach would facilitate faster recruitment, ultimately accelerating the generation of results from clinical trials.

The importance of proactive multinational trial networks

The CT-CURE Consortium recommends that broad networks of academic sponsors be prepared to establish basic multinational platform trials for defined scenarios, such as specific symptoms or pathogen classes, well in advance of emerging public health threats. One potential approach could involve authorizing these studies before a crisis fully develops, with a partial initial submission that includes only Part I documents. These trials could be approved with the condition that a Part I and Part II substantial modification application must submitted and authorised when the trial needs to be activated before trial subjects are recruited and included. Since epidemiology of future public health emergencies is not known, such clinical trial networks should ideally include all EU/EEA Member States from the outset or have the capacity to rapidly expand once the trial is initiated. This is crucial as it is difficult to predict which Member States will be most affected by a future public health emergency.

Finally, while rapid decisions on clinical trial applications are essential in public health emergencies, they must be accompanied by other measures to facilitate the swift inclusion of trial subjects. This includes funding academic networks that prepare multinational public health emergency trials and simplifying procedures for setting up trial site contracts. According to the public search database for authorized trials in the EU/EEA, two initial CT-CURE trials did not begin recruitment until 81 and 197 calendar days after the initial trial application was authorized. Interestingly, the MSC that approved the application last was the first to include subjects in the trial. In contrast, the RECOVERY Collaborative Group reported that the first subject was enrolled just days after the application was approved.

ENSURING THE SUSTAINABILITY OF CT-CURE'S EXPEDITED ASSESSMENT EXPERIENCE FOR MULTINATIONAL CLINICAL TRIALS IN PUBLIC HEALTH EMERGENCIES

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